DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 14 1999

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The Honorable Orrin G. Hatch
United States Senate
Washington, D.C. 20510-4402

Dear Senator Hatch:

Thank you for your continued interest in dietary supplements. This is in response to your February 4, 1999 letter regarding the Food and Drug Administration's (FDA or the Agency) current efforts to implement the Dietary Supplement Health and Education Act (DSHEA). In your letter, you asked several questions that relate to the proposed rule on dietary supplements containing ephedrine alkaloids (62 FR 30678, June 4, 1997) and you requested a briefing for your staff. As you may know, FDA met with your staff on February 25, 1999. At that meeting, your staff requested that FDA also provide specific information related to the proposed rule. Your questions are summarized below, followed by FDA's responses. The information requested by your staff follows your questions. A similar letter has been sent to your cosigner, Senator Tom Harkin.

(1) FDA's proposal to restrict serving size to 8 mg per serving appears to be based on 13 adverse event reports (AER's). FDA acknowledges that the [8 mg.] potency limits may result in little or no reduction in the expected number of adverse events reports. 62 FR at 30706-7: see also id. at 30708 (Table 7). Given the estimates of billions of servings that have been provided to the Agency, are 13 AER's quantitatively sufficient, based on reasonable estimates of consumption for these products, to establish a causal relationship on which to base a serving limitation for dietary supplements containing ephedrine alkaloids? Has the Agency ever used such a proportionately small number of AER's to establish a serving limit for any other widely consumed food or dietary supplement product?

The proposed serving limits were based on multiple sources of information, which included a review of clinical trials, consumer use patterns, the adverse event reports (AER's), and FDA's scientific evaluation. Information from the review of the clinical trials suggests that adverse events can occur with the use of 20 milligrams (mg) of ephedrine. FDA's scientific evaluation documents that ephedrine alkaloids,

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including those from botanical sources, can cause adverse events, such as increases in blood pressure, arrhythmia, psychosis, heart attack, stroke, and seizure. The data also suggest that the likelihood, frequency, and severity of the adverse events may be increased by such factors as sensitivity to the ephedrine alkaloids; additive or interactive effects from the mixtures of different ephedrine alkaloids, such as those contained in botanical sources of ephedrine alkaloids (e.g. *Ephedra sinica*); and other ingredients contained in the product that act synergistically with the ephedrine alkaloids (e.g., caffeine). Because of these factors, adverse events may occur in many individuals even with relatively low intakes, including intake levels lower than the dosage of ephedrine used in over-the-counter products (e.g., drugs).

Recognizing that adverse events could be expected to occur at the relatively low intakes of the ephedrine alkaloids, FDA reviewed the AER's where the dietary supplement products had been collected and analyzed for their ephedrine alkaloid content. Data from this review showed that the serious or clinically significant adverse events, including life-threatening adverse events, occurred at levels approaching and above 10 mg of ephedrine alkaloids per serving and continued through intakes over 50 mg of ephedrine alkaloids per serving. To summarize data at the lower bound of intake levels at which clinically significant and serious AER's had occurred, FDA prepared a table (Ref. 149a) that includes descriptions of the thirteen AER's that were associated with products that contained less than 20 mg ephedrine alkaloids per serving. The available data, including the AER's and the known physiological and pharmacological effects of ephedrine, are sufficient to show that clinically serious, including life-threatening, adverse events associated with the use of ephedrine alkaloids can reasonably be expected to occur at intake levels as low as 10 mg ephedrine alkaloids per serving. To compensate for uncertainties, FDA proposed that 8 mg or more of ephedrine alkaloids per serving in a dietary supplement is unsafe.

Importantly, the Working Group of the Food Advisory Committee and several members of the Food Advisory Committee recommended that FDA establish single serving and daily use limits for ephedrine alkaloids contained in dietary supplements. FDA's proposed serving and daily limits generally are consistent with many of the members' recommendations.

(2) Ohio, Washington, Florida, and Texas legally market dietary supplements containing ephedrine alkaloids if formulated to contain no more than 25 mg. per serving and if

the product label does not recommend consumption of more than four servings per day (up to 100 mg. per day).

(a) In states that have adopted this standard, does the FDA have detailed, credible information regarding any significant number of adverse events being reported since such a standard was put into effect? If so, please furnish such information?

Since the Ohio law became effective on March 31, 1997 (section 3719.44(K)(2)(a) of the Ohio Revised Code), the Agency has received six AER's associated with dietary supplements thought to contain ephedrine alkaloids where the individual who reported the adverse event was identified as being in the State of Ohio (ARMS Nos. 12368, 12698, 12946, 13001, 13081, 13165). The AER's describe a range of symptoms, including dizziness and other such effects (two individuals); seizure (one individual); psychological problems including hallucinations (one individual); rash on face and hands (one individual); and cardiac arrhythmias (one individual).

Most of these reports lack information necessary to determine whether the adverse event occurred in Ohio or whether the product was purchased or used in Ohio: two of the AER's appear to be from the injured party who gave an address in Ohio; three of the six reports came from a health professional who gave an office address in Ohio; the last report came from a woman in Ohio who reported an adverse event on behalf of her daughter, but the report did not specify where the daughter was when she bought and consumed the product.

The Texas regulation and the Florida law were recently adopted and thus, adequate time has not passed to collect information on AER's that may have occurred since the adoption of the 25 mg standard by these states. The Washington law (Washington Annotated Code 246-883-030(3)) permits the sale of botanical products of the genus Ephedra containing 25 mg or less ephedrine per serving. Because botanical products from the genus Ephedra contain a mixture of ephedrine alkaloids and the 25 mg limit applies only to ephedrine, the law actually permits the sale of dietary supplement products containing more than 25 milligrams ephedrine alkaloids. Therefore, Washington has adopted a different standard than Ohio, Texas, and Florida.

(b) Has FDA analyzed the trend in AER's to determine whether the number of scientifically reliable AER's (as opposed to AER's that are missing essential information, or are clearly unrelated to product consumption) has

or are clearly unrelated to product consumption) has changed since the 25 mg per serving, 100 mg per day standard was adopted by major segments of the industry?

If, as your question suggests, major segments of the industry have adopted the 25 mg ephedrine alkaloids per serving, 100 mg per day standard, this raises particular concern because that would mean manufacturers are increasing the amounts of ephedrine alkaloids contained in their products. The majority of the products collected during the Agency's review of ephedrine alkaloid-containing dietary supplements in the marketplace contained less than 25 mg ephedrine alkaloids per serving. During the 1996 meeting of FDA's Food Advisory Committee, representatives of the dietary supplement industry advocated the use of much lower levels of ephedrine alkaloids in dietary supplements (e.g., 12 mg ephedrine alkaloids per serving).

In response to your question, while we have not specifically analyzed the AER's for a trend in serving amounts, the Agency has received over 120 AER's since the proposed rule was published. At least half of these AER's are for serious adverse events, including heart attack, stroke, and seizure. Although the actual number of AER's reported to FDA has decreased, the ratio of serious AER's relative to the total number reported has increased. Presently, FDA is in the process of obtaining follow-up information (e.g., medical records, product label and labeling, consumer use information) to allow a more in-depth evaluation of these newer reports. In light of the number and the seriousness of the new AER's, the Agency remains very concerned about the public health risks associated with the use of ephedrine alkaloid-containing dietary supplements in the marketplace.

(c) Taking those reports for which there is sufficient reliable information to make a determination that the reported event was likely caused by the products at issue, has FDA compared the number of AER's the Agency has received in the 12 month period since the comment period for this rule was closed (December 1997 through December 1998) to similarly reliable AER's for the other 12 month periods, or has the Agency taken any other steps to attempt to assess the impact of industry's adoption of the 25 mg/100 mg. standard?

While FDA has not conducted precisely this kind of analysis, the Agency continues to monitor AER's associated with the use of ephedrine alkaloid-containing dietary supplements. As

discussed in the answer to question 2(b) above, since the proposed rule was published, the Agency has received over 120 AER's, at least half of which are for serious adverse events. In part for this reason, the Agency remains concerned about the public health risks associated with the use of dietary supplements containing ephedrine alkaloids at the level you cite as the industry standard. In the proposed rule, FDA presented scientific literature suggesting that the use of 20 mg and above of ephedrine is unsafe. The Agency also presented evidence on the marked sensitivity of some individuals to the effects of ephedrine alkaloids and on other factors that may serve to increase the likelihood, frequency, or severity of adverse events with the use of relatively low levels of ephedrine alkaloids. FDA documented that life-threatening adverse events have been associated with the use of dietary supplements containing as low as 10 milligrams of ephedrine alkaloids per serving. In light of these data, the state laws permitting the sale of dietary supplements containing 25 mg of ephedrine alkaloids per serving raise serious public health concerns because such supplements contain ephedrine alkaloids at a level at which serious adverse events would reasonably be expected to occur.

During a meeting with your staff on February 25, 1999, your staff requested the opinions of industry consultants who disagreed with the causality assessment by Theodore Farber, Ph.D., who was retained by Starlight International, Ltd. and Nutraceutical Corporation to review the AER's associated with ephedrine alkaloid-containing dietary supplements.

In response to the proposed rule, the Agency received several comments that contained assessments from medical and scientific consultants who evaluated whether the AER's, or selected AER's, could be related to the use of ephedrine alkaloids.

Michael Davidson, M.D., F.A.C.C., was retained by the National Nutritional Foods Association to review adverse event reports associated with dietary supplements containing ephedrine alkaloids. In his letter to FDA, Dr. Davidson expresses the opinion that herbal products should not be regulated under DSHEA because of their physiologic effects and significant potential for toxicity. Dr. Davidson recommends that an appropriate regulatory category be established for botanicals and that safety assessments be required before herbal products are marketed. He warns that problems similar to those that have been associated with dietary supplements containing ephedrine alkaloids may occur in the future with other products. A copy of Dr. Davidson's letter is enclosed.

John Wurpel, Ph.D., reviewed a series of AER's associated with dietary supplements containing ephedrine alkaloids. In a report submitted to FDA by the Dietary Supplement Safety and Science Coalition (DSSSC), Dr. Wurpel lists several cases in which ephedrine was likely to elicit an untoward event (e.g., ARMS No. 11313 (anaphylaxis); ARMS No. 11307 (cardiac arrest); ARMS No. 11308 (stroke); ARMS No. 11008 (cardiac arrest resulting in death); ARMS No. 11018 (myocardial infarction); ARMS No.11186 (cardiac arrest). Dr. Wurpel's assessment disagrees with Dr. Farber's judgment on the causal role of ephedrine in the same AER's (which was ARMS No. 11313, low possible; ARMS No. 11307, low possible; ARMS No. 11308, improbable; ARMS No. 11008, probable overdose; ARMS No. 11018, improbable; ARMS No. 11186, possible. Relevant pages from Dr. Wurpel's statement are enclosed.

Importantly, FDA did not decide whether or not a particular adverse event was caused by the use of an ephedrine alkaloid-containing dietary supplement. FDA considered such attribution was best made by the physicians and pathologists (medical examiners) providing direct patient care and evaluation. In many of the AER's, physicians and medical examiners directly involved with the care or evaluation of a particular consumer made a finding that the use of an ephedrine alkaloid-containing dietary supplements caused, or contributed to, the adverse event, including irregular heart beat, hypertensive crisis, altered behavior, psychosis, stroke, seizure, heart attack, and cardiomyopathy leading to death.

We hope this information is helpful. If we may be of any further assistance, please let us know.

Sincerely,

Melinda K. Plaisier
Interim Associate Commissioner
for Legislative Affairs

cc: Dockets Management Branch

2 Enclosures

United States Senate

WASHINGTON, D.C. 20510

February 4, 1999

Jane Henney, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane, Room 1471
Rockville, Maryland 20857

Dear Dr. Henney:

As you know, we have worked to assure that Americans have access to safe and healthful dietary supplement products. Further, in writing the Dietary Supplement Health and Education Act (DSHEA), we have worked to assure that the Food and Drug Administration (FDA) has the power to take unsafe supplements off the shelves. As the agency issues regulations to implement DSHEA, we are very interested in the scientific rationale the agency employs in justifying its proposed regulatory actions. We would greatly appreciate it if you could arrange for your staff to brief our staffs on the agency's current efforts to implement DSHEA, including the status of the good manufacturer practices, structure/function, and ephedrine alkaloids regulations. To make this briefing more productive, we have identified several questions pertaining to FDA's June 4, 1997 proposed rule on dietary supplements containing ephedrine alkaloids:

(1) FDA's proposal to restrict serving size to 8 mg. per serving appears to be based on 13 adverse event reports (AERs). The proposal acknowledges that "the [8 mg.] potency limits may result in little or no reduction in the expected number of adverse event reports." 622 Fed. Reg. At 30706-7: see also id. at 30708 (Table 7). Given the estimates of billions of servings that have been provided to the agency, are 13 AERs quantitatively sufficient, based on reasonable estimates of consumption for these products, to establish a causal relationship on which to base a serving limitation for dietary supplements containing ephedrine alkaloids? Has the agency ever used such a proportionately small number of AERs to establish a serving limit for any other widely consumed food or dietary supplement product?

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(a) In states that have adopted this standard, does the FDA have detailed, credible information regarding any significant number of adverse events being reported since such a standard was put into effect? If so, please furnish such information.

(b) Has FDA analyzed the trend in AERs to determine whether the number of scientifically reliable AERs (as opposed to AERs that are missing essential information, or are clearly unrelated to product consumption) has changed since the 25 mg. per serving, 100 mg. per day standard was adopted by major segments of the industry?

(c) Taking those reports for which there is sufficient reliable information to make a determination that the reported event was likely caused by the products at issue, has FDA compared the number of AERs the agency has received in the 12 month period since the comment period for this rule was closed (December 1997 through December 1998) to similarly reliable AERs for the other 12 month periods, or has the agency taken any other steps to attempt to assess the impact of industry's adoption of the 25 mg./100 mg. standard?

In order to give us and our staffs an opportunity to consider your responses before your agency reaches any final conclusions on this matter, we would appreciate it if you could arrange that this staff briefing occur by February 15, 1999. Thank you for your attention to my request. If you or your staff have and questions related to my request, please call Peter Reinecke at (202) 224-3254 to arrange for this briefing.

Sincerely,

Tom Harkin
United States Senator

Orrin G. Hatch
United States Senator